BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

Policy #: 337
Latest Review Date: July 2024
Category: Medicine

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

In accordance with Title XVIII of the Social Security Act, Section 1862 (a)(10) cosmetic surgery or expenses incurred in connection with such surgery are not covered except as required for the prompt repair of accidental injury or for improvement of the functioning of a malformed body member.

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat one or more courses of **photodynamic therapy** as a **covered** benefit for **any** of the following oncologic applications:

- Palliative treatment of obstructing esophageal cancer; **OR**
- Palliative treatment of obstructing endobronchial lesions; **OR**
- Treatment of early-stage non-small cell lung cancer in individuals who are ineligible for surgery and radiation therapy; **OR**
- Treatment of high-grade dysplasia in Barrett's esophagus; **OR**
- Palliative treatment of unresectable cholangiocarcinoma when used with stenting

Blue Advantage will treat **other oncologic applications of photodynamic therapy** including, but not limited to, other malignancies and Barrett's esophagus without associated high-grade dysplasia as a **non-covered** benefit and as **investigational**.

Note: This policy does not address the use of photodynamic therapy as a treatment of age-related macular degeneration or actinic keratoses. See CMS NCD for Ocular Photodynamic Therapy (OPT) (80.2) and NCD for Treatment of Actinic Keratosis (AKs) (250.4).

Additionally, this policy does not address extracorporeal photopheresis. NCD for Extracorporeal Photopheresis (110.4).

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contracts and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Photodynamic therapy (PDT; also called phototherapy, photo-radiotherapy, photosensitizing therapy, or photo-chemotherapy) is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance. Treatment for tumor cells occurs through selective retention of the photosensitizing agent and the selective delivery of light.

Photodynamic Therapy
Photodynamic therapy (PDT) has been investigated for use in a wide variety of tumors, including esophageal, lung, cholangiocarcinoma, prostate, bladder, breast, brain (administered intraoperatively), skin, and head and neck cancers. Barrett's esophagus also has been treated with PDT.

Several photosensitizing agents have been used in PDT: porfimer sodium (Photofrin®), administered intravenously 48 hours before light exposure, and 5-aminolevulinic acid (5-ALA), administered orally 4 to 6 hours before the procedure. Aminolevulinic acid is metabolized to protoporphyrin IX, which is preferentially taken up by the mucosa. Clearance of porfimer occurs in a variety of normal tissues over 40 to 72 hours, but tumor cells retain porfimer for a longer period. Laser treatment of Barrett's esophagus may be enhanced by the use of balloons containing a cylindrical diffusing fiber. The balloon compresses the mucosal folds of the esophagus, thus increasing the likelihood that the entire Barrett mucosa is exposed to light. All patients who receive porfimer become photosensitive and must avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days.

KEY POINTS:
The most recent update with literature review covered the period through May 30, 2024. Most studies from outside the U.S. use photosensitizing agents that have not been cleared for use in the U.S.

Summary of Evidence
For individuals who have obstructing esophageal cancer who receive photodynamic therapy (PDT) as palliation, the evidence includes systematic reviews, randomized controlled trials (RCTs), and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. A meta-analysis comparing PDT with neodymium-doped yttrium aluminum garnet (Nd:YAG) laser suggested that improvements in dysphagia are similar, although estimates are imprecise. Compared with the neodymium-doped yttrium aluminum garnet laser, PDT is associated with a lower risk of perforation and a higher risk of adverse reactions to the light (e.g. photosensitivity). PDT plus argon plasma coagulation appears to prolong the time to recurrence of dysphagia as opposed to argon plasma coagulation alone. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have obstructing endobronchial lesions who receive PDT as palliation, the evidence includes (RCTs) and uncontrolled single-arm studies. Relevant outcomes are changes in disease status, symptoms, quality of life, and treatment-related morbidity. Evidence from RCTs comparing PDT with neodymium-doped yttrium aluminum garnet laser has generally supported reductions in symptoms using PDT similar to those using a laser. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have early-stage non-small-cell lung cancer (NSCLC) who are not candidates for surgery or radiotherapy who receive PDT, the evidence includes uncontrolled single-arm studies. Relevant outcomes are overall survival (OS), disease-specific survival,

change in disease status, quality of life, and treatment-related morbidity. There are few patients with early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy. While several treatment methods (eg, laser, electrocautery, cryotherapy, brachytherapy) are available for this population, studies comparing the treatment methods are not available. Case series of PDT include between 21 and 95 patients and have reported complete response rates ranging from 72% to 100%. Given the small size of this potential population and the ineligibility for standard surgical treatment or radiotherapy, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Barrett's esophagus with high-grade dysplasia who receive PDT, the evidence includes 2 systematic reviews and 2 RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. One RCT compared PDT plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression with cancer persisting during 5 years of follow-up for patients in the PDT plus proton pump inhibitor group. The results of the RCT also revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Another RCT compared PDT performed with different photosensitizers; results revealed that neither were valuable long-term treatments for dysplastic Barrett esophagus. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable cholangiocarcinoma who receive PDT plus stenting as palliation, the evidence includes systematic reviews, RCTs, and observational studies. Relevant outcomes are changes in disease status, symptoms, quality of life, and treatment-related morbidity. Three small RCTs and several observational studies have found that PDT plus stenting is associated with the greater elimination of bile duct stenosis and improved survival benefit compared with stenting alone. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival, but not OS, with similar adverse event rates. Case series have suggested an improvement in the quality of life with PDT. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small size of this potential population, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other malignancies (eg, gynecologic, bladder, head and neck, brain, soft tissue) who receive PDT, the evidence includes controlled observational studies and uncontrolled single-arm studies. Relevant outcomes are OS, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The published literature on PDT for these malignancies is generally comprised of small case series without comparator groups. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Chest Physicians

In 2013, ACCP updated its evidence-based practice guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways. The College recommended PDT and other endobronchial treatments (brachytherapy, cryotherapy, electrocautery) "for patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection." (Grade 1C: strong recommendation based on low-quality evidence) The guidelines summarized the evidence for PDT in early lung cancer as follows:

"PDT appears to be an effective therapeutic modality for small early stage centrally located lung cancers, the majority of which are squamous cell carcinomas. Complete response (CR) rates have been achieved in 32% to 100% of cancers, with the longitudinal length of the cancer being an important predictor of response. However, some patients experience local recurrences, and long-term outcomes remain suboptimal. Talaporfin sodium (NPe6), a newer-generation photosensitizer, appears to be as effective but better tolerated than older agents. However, these data have only been reported by one group and need to be validated in larger numbers of patients."

American Gastroenterological Association

The 2011 American Gastroenterological Association's (AGA) position statement on Barrett esophagus management recommended PDT as an option for the treatment of confirmed HGD with Barrett esophagus. In 2020, the AGA published a clinical practice update on the endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer. The practice update provides a best practice statement that states that endoscopic therapy, which may include ablative therapies such as PDT, is the preferred treatment for Barret esophagus with HGD. In 2021, the AGA released an expert review clinical practice update on the optimal management of malignant alimentary tract obstruction. It stated that "For patients who present with esophageal obstruction from esophageal cancer who are not candidates for resection, clinicians should consider either SEMS [self-expanding metal stent] insertion or brachytherapy as sole therapy or in combination. Clinicians should not consider the use of laser therapy or photodynamic therapy because of the lack of evidence of better outcomes and superior alternatives."

American College of Gastroenterology

The 2016 American College of Gastroenterology guidelines on diagnosis and management of Barrett's esophagus stated that there is Level I evidence for prevention of cancer for PDT and radiofrequency ablation in Barrett's esophagus with high-grade dysplasia. The guidelines also stated: "Given the costs and side-effect profile of photodynamic therapy, as well as the large body of data supporting the safety and efficacy of radiofrequency ablation, this modality appears to be the preferred therapy for most patients." The 2021 updated guidelines make the following recommendation related to endoscopic therapy: "We suggest endoscopic therapy in patients with BE [Barrett's esophagus] confirmed with LGD [low-grade dysplasia] to reduce the risk of progression to HGD/EAC [esophageal adenocarcinoma], with endoscopic surveillance of confirmed LGD as an acceptable alternative (strength of recommendation: conditional; quality of evidence: moderate)." However, the guideline does not specifically mention PDT and only mentions radiofrequency ablation in the context of endoscopic therapy.

National Comprehensive Cancer Network
Esophageal Cancer and Barrett Esophagus
The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2024) for esophageal cancer state that RFA has become the preferred treatment while photodynamic therapy is an alternative strategy for patients who have Barrett esophagus with high-grade dysplasia. Regarding palliative PDT, they note that "long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG [neodymium-doped yttrium aluminum garnet] laser, PDT, and cryoablation, or endoscopic and radiographic-assisted insertion of expandable metal or plastic stents." Regarding palliative PDT, they note that "long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG [neodymium-doped yttrium aluminum garnet] laser, PDT, and cryoablation, or endoscopic and radiographic-assisted insertion of expandable metal or plastic stents." The guidelines also state that PDT can effectively treat esophageal obstruction but "is less commonly performed due to photosensitivity and costs" compared with radiation and brachytherapy.

Cholangiocarcinoma
NCCN guidelines on biliary tract cancers (v.2.2024) describe PDT as a relatively new therapy for local treatment of unresectable cholangiocarcinoma, stating that the combination of PDT and biliary stenting "was reported to be associated with prolonged overall survival in patients with unresectable cholangiocarcinoma based on 2 small randomized clinical trials [Ortner et al (2003) and Zoepf et al (2005)]."

Non-Small Cell Lung Cancer
The NCCN guideline (v.5.2024) on non-small cell lung cancer (NSCLC) states that PDT is a treatment option in patients with locoregional recurrence of non-small cell lung cancer with endobronchial obstruction or severe hemoptysis.

National Institute for Health and Care Excellence
The NICE has published guidance on a number of applications of PDT

- Guidance for palliative treatment of advanced esophageal cancer, treatment of localized inoperable endobronchial cancer, and treatment of advanced bronchial carcinoma has indicated that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE guidance has indicated that PDT should not be used for the following 3 indications due to poor quality evidence: interstitial photodynamic therapy for malignant parotid tumors, early-stage esophageal cancer, and bile duct cancer.
- NICE guidance has indicated that PDT may be considered for Barrett esophagus with flat HGD, taking into account the evidence of their long-term efficacy, cost, and complication rates. The guidance notes that current evidence on the use of PDT for Barrett esophagus with either low-grade dysplasia or no dysplasia is inadequate so that the balance of risk and benefit is unclear.
- NICE guidance on PDT for brain tumors has indicated that current evidence is limited in quality and quantity, and the procedure should only be used in context of RCTs with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality of life outcomes.

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:
Hematoporphyrin, Photodynamic Therapy; photochemotherapy, phototherapy, photoradiotherapy, Oncologic Applications, Photofrin, Photoradiation Therapy, Photosensitizing Therapy, PDT, NPc6, Foscan, meta-tetrahydroxyphenylchorin, Barrett Esophagus

APPROVED BY GOVERNING BODIES:
Labeled indications for porfimer sodium (Photofrin®; Pinnacle Biologics), as approved by the U.S. Food and Drug Administration (FDA) are as follows:

Esophageal Cancer
- Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy

Endobronchial Cancer
- Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer (NSCLC).
- Treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated.

High-grade Dysplasia in Barrett's Esophagus
- Treatment of high-grade dysplasia in Barrett esophagus who do not undergo esophagectomy

As of May 2024, oral 5-aminolevulinic acid (5-ALA) has not received FDA approval as a photosensitizing agent for PDT. It is currently only indicated as an adjunct for the visualization of malignant tissue during surgery in individuals with glioma. Topical 5-ALA used for treatment of actinic keratoses is addressed separately.

This policy only addresses the non-dermatologic oncologic applications of photodynamic therapy and does not address its use in dermatologic applications, such as actinic keratosis (see policy #050 Dermatologic Applications of Photodynamic Therapy), and superficial basal cell cancer or age-related macular degeneration (see policy #047 Photodynamic Therapy, Ocular; Visudyne). In addition, photodynamic therapy should not be confused with extracorporeal photopheresis, which involves withdrawing blood from the patient, irradiating it with ultraviolet light, and then returning the blood to the patient. Extracorporeal photopheresis is addressed separately, (see policy #028 Extracorporeal Photopheresis).

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT codes:

31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (e.g., laser therapy, cryotherapy)
43229	Esophagoscopy, Flexible, Transoral; With Ablation of Tumor(s), Polyp(s) or Other Lesion(s), (Includes Pre and Post-dilation and Guide Wire Passage, When Performed)
96570	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via application of photosensitive drug(s); first 30 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
96571	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via application of photosensitive drug(s); each additional 15 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)

HCPCS:

J9600	Porfimer Sodium, 75 mg

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POLICY HISTORY:

Adopted for Blue Advantage, January 2009
Available for comment January 27-March 12, 2009
Medical Policy Group, March 2010
Medical Policy Group, March 2012
Medical Policy Group, April 2013
Medical Policy Group, March 2015
Medical Policy Group, April 2015
Medical Policy Group, August 2017
Available for comment August 30 through October 13, 2007
Medical Policy Group, August 2018 **(2):** Updates to Description, Key Points, and References. No change in policy statement. Added Key Words (phototherapy, photoradiotherapy, Barrett esophagus). Removed previous coding section prior to 12/31/13.
Medical Policy Group, July 2019
Medical Policy Group, July 2020
Medical Policy Group, July 2021
Medical Policy Group, July 2022
Medical Policy Group, July 2023
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, July 2024
UM Committee, July 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.